REMARKS

Claim 1-29 are pending. Claims 1, 2, 8, 9, 27 and 28 have been amended. New claims 30-32 have been added.

Claims 1, 8, 27 and 28 have been amended to include the transition phrase "consisting essentially of." Claims 2 and 9 have been amended to include "ftorafur" as an alternative name for TS-1 and to insert "-" before "FU.". Support for amended claims 2 and 9 can be found in the specification at page 9, lines 3-4. Claim 8 has been amended to clarify that the 5-FU prodrug is administered to a patient with psoriasis. Support for amended claim 8 can be found in the specification at page 7, lines 19-21. Claims 27 and 28 have been amended to clarify that the 5-FU prodrug is administered to a patient with an inflammatory skin condition. Support for amended claims 27 and 28 can be found in the specification at page 9, lines 3-15.

Support for new claim 30 can be found in the specification at page 7, lines 15-16; page 8, lines 3-4; and page 9, lines 3-10. Support for new claim 31 can be found in the specification at page 7, lines 16-17. Support for new claim 32 can be found in the specification at page 14, lines 8-13.

Objections to the claims

The examiner has objected to claims 2 and 9 because the abbreviations "TS-1" and "FdUMP" are not preceded in their first occurrence by the terms represented by the abbreviations, and for omission of "-" before "FU." The specification identifies alternative names for TS-1 such as ftorafur and S-1. Claims 2 and 9 have been amended to include ftorafur at the first occurrence of TS-1 and a hyphen before FU. The term abbreviated by FdUMP is well-known in the art as the abbreviation for 5-fluoro-2'-deoxyuridine-5'-monophosphate. See, for example, van der Wilt, et al., Biochem Pharmacol. 2002 Aug 15;64(4):669-75 (abstract) (copy enclosed herewith).

Accordingly, the claim objections should be withdrawn.

Rejections of claims 1-29 under 35 U.S.C. § 112, second paragraph

Claims 1-29 have been rejected as indefinite because the examiner contends that these claims omit an essential element, namely a pharmaceutical carrier. This rejection is respectfully traversed. The specification defines "prodrug" as "a pharmacologically inactive compound that is converted into a pharmacologically active agent by a metabolic transformation. *In vivo,* a prodrug is acted on by naturally occurring enzyme(s) resulting in liberation of the pharmacologically active agent" (specification, page 5, lines 2-4). Thus, implicit in "prodrug" is the ability to be absorbed and metabolized into the active agent in a patient's body. As disclosed in the specification, a pharmaceutical carrier is only an optional additive (specification, page 12, lines 1-2). A prodrug, as defined in the specification, does not require a pharmaceutical carrier to effectively treat a patient's condition. Accordingly, this rejection should be withdrawn.

The examiner contends that claims 8, 27 and 28 (and their dependent claims) are indefinite because it is unclear to whom the 5-FU prodrug is being administered. Claim 8 has been amended to specify that the 5-FU prodrug is administered to a patient with psoriasis. Claims 27 and 28 have been amended to specify that the 5-FU prodrug is administered to a patient with an inflammatory skin condition. Accordingly, this rejection should be withdrawn.

Rejection of claims 1-29 under 35 U.S.C. § 103(a)

Claims 1-29 stand rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,654,286 ("Hostetler") in view of U.S. Patent No. 6,297,223 ("Spector") in combination with U.S. Patent No. 6,664,242 ("Bissery").

The examiner alleges that Hostetler discloses the topical treatment of skin hyperproliferative diseases such as psoriasis using a nucleoside analog phosphate ester and related analogs (e.g., 5-fluorouracil phosphate ester). Hostetler discloses that topical 5-FU has not been very successful for the treatment of skin inflammation (Hostetler, col. 1, lines 62-65). The examiner acknowledges that Hostetler does not disclose a prodrug of 5-fluorouracil and its oral use in the treatment of psoriasis (Office Action, page 4).

The examiner contends that Spector discloses oral administration of a prodrug of 5-fluorouracil for the treatment of psoriasis or rheumatoid arthritis, and a dosage range of 0.1 to 3000 mg per kilogram of body weight. Spector does not disclose capecitabine. According to the examiner, Bissery discloses that capecitabine has anti-neoplastic activity and a more favorable safety profile than 5-FU. *See* Office Action, pages 4-5.

The examiner alleges that one of ordinary skill in the art would have a reasonable expectation for success in combining these references to arrive at a method for treating an inflammatory skin condition such as psoriasis in a patient by orally administering an effective amount of a prodrug of 5-FU. According to the examiner, the motivation to combine these references is provided by Hostetler ("Hostetler discloses that the topical use of 5-fluorouracil has not been very successful in the treatment to reduce skin inflammation") and Spector ("Spector discloses the oral use of a prodrug of 5-fluorouracil in the treatment of psoriasis or rheumatoid arthritis"). *See* Office Action, pages 5-6.

In a rejection for obviousness, the motivation to combine the teachings must come from the references themselves. *See, e.g., In re Gordon,* 733 F.2d 900 (Fed. Cir. 1984). The references do not provide such motivation.

According to Hostetler: "[t]opical 5-fluorouracil has been used with some success but the treatment causes severe erythema, edema, bullae formation and ulceration of the skin in treated areas and therefore is not well accepted by patients" (Hostetler, col. 1, lines 62-65). Thus, Hostetler teaches that topical 5-FU is <u>not</u> a good treatment for psoriasis. Nothing in Hostetler suggests that using a different drug (i.e., a 5-FU prodrug) by a different route of administration (i.e., oral) would be effective to treat skin inflammation. Claims 1-29 require a 5-FU prodrug. Claims 1-26 require both an oral route of administration and a 5-FU prodrug. Far from providing motivation to explore 5-FU-like drugs further, Hostetler discourages one of ordinary skill in the art from doing so.

Spector discloses that a prodrug of 5-FU *in combination with* a uracil derivative *may* be useful for the treatment of psoriasis (Spector, col. 1, lines 53-57). Spector does <u>not</u> disclose or suggest that a prodrug of 5-FU as the only active agent can effectively treat psoriasis. In fact, Spector discloses that an orally administered 5-FU prodrug, when given without a uracil derivative,

is not absorbed but rather is destroyed in the gastrointestinal tract. "[I]t has now been found that if a 5-substituted uracil derivative ... is administered prior to oral administration of 5-FU *(or a prodrug thereof)*, high and persistent levels of 5-FU are obtained in the plasma, indicating that this compound is not being destroyed." Spector does not disclose capecitabine.

Bissery does not disclose or suggest the use of capecitabine, or any other prodrug of 5-FU, for the treatment of an inflammatory skin condition. Inflammatory skin conditions, including psoriasis, are not neoplasms.

In sum, Hostetler discloses that topical 5-FU is not useful for the treatment of psoriasis, Bissery discloses that capectabine has anti-neoplastic activity, and Spector discloses that certain prodrugs of 5-FU can be useful for the treatment of inflammatory skin conditions if they are administered with a specific compound. Thus, even if there was a motivation to combine, no combination of these references suggests the use of a 5-FU prodrug alone for the treatment of an inflammatory skin condition or psoriasis.

Spector speculates that a 5-FU prodrug in combination with a specific compound may be useful to treat psoriasis (Spector, col. 1, lines 51-57). Spector lists certain 5-FU prodrugs (Spector, col. 2, lines 38-43), but not capecitabine. According to Bissery, capecitabine has a mechanism of action that is unique among the 5-FU prodrugs (Bissery, col. 4, lines 5-23). Thus, one of ordinary skill in the art would not have a reasonable expectation that treating a patient with an inflammatory skin condition or psoriasis with capecitabine, alone or in combination with an additional active agent, would be successful.

Accordingly, this rejection should be withdrawn.

Conclusion

No new matter has been added by these amendments. In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: July 5, 2005

Respectfully submitted,

By _____

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Applicant